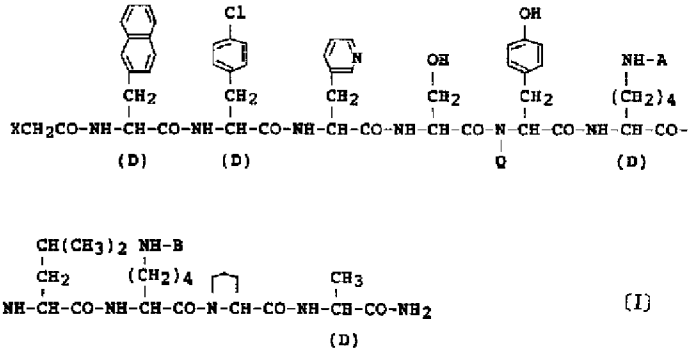
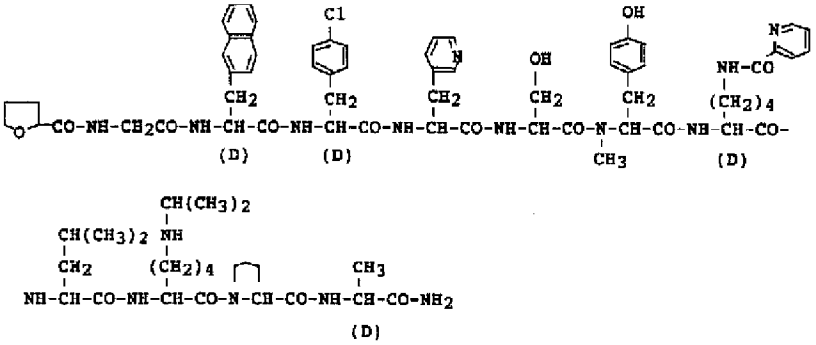
CLAIMS

[Claim(s)]
[Claim 1]A formula[Formula 1]

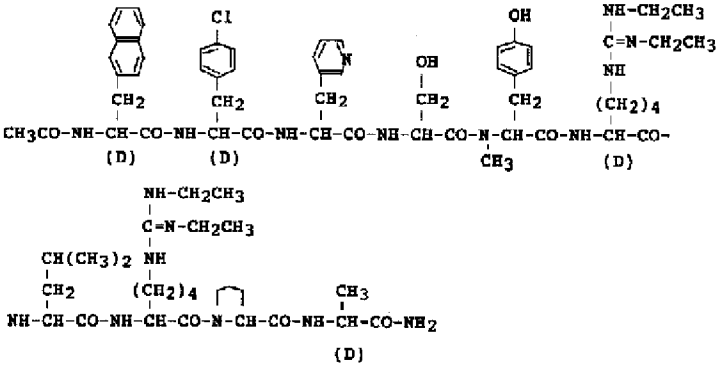


[Q among a formula hydrogen or tetrahydro furil carboxamide X hydrogen or methyl, The liquid containing the bioactive peptide expressed with A showing nicotinoyl or N,N'-diethyl amidino, and B showing isopropyl or N,N'-diethyl amidino] or its salt is made into the inner aqueous phase, A manufacturing method of the sustained release drug manufacturing the W/O type emulsified matter which makes an oil phase the solution containing the biodegradation nature polymer which has a carboxyl group of isolation at the end, adding the emulsified matter subsequently obtained to an outer water phase, and manufacturing a W/O/W type emulsified matter.
[Claim 2]The manufacturing method according to claim 1 whose biodegradation nature polymer is aliphatic polyester.
[Claim 3]The manufacturing method according to claim 2 whose aliphatic polyester is a lactic acid-glycolic acid copolymer.
[Claim 4]The manufacturing method according to claim 3 whose composition ratios (mol %) of lactic acid of a lactic acid-glycolic acid copolymer and glycolic acid are about 100/0 thru/or about 40/60.
[Claim 5]The manufacturing method according to claim 3 whose weight average molecular weight of a lactic acid-glycolic acid copolymer is about 5,000 thru/or about 20,000.
[Claim 6]The manufacturing method according to claim 1 whose concentration of bioactive peptide in inner aqueous phase is about 0.1 thru/or about 150% (W/V).
[Claim 7]The manufacturing method according to claim 1 whose concentration of biodegradation nature polymer in an oil phase is about 0.1 thru/or about 80% (W/W).
[Claim 8]The manufacturing method according to claim 1 whose quantitative ratios of inner aqueous phase to an oil phase are about 1 thru/or about 50% (V/V).
[Claim 9]The manufacturing method according to claim 1 it is about 1 of oil phase

volume thru/or about 10,000 times whose volume of an outer water phase of this.
[Claim 10]The manufacturing method according to claim 1 whose sustained release drug is a microcapsule.
[Claim 11]The manufacturing method according to claim 1 whose X is 2-tetrahydro furil carboxamide.
[Claim 12]The manufacturing method according to claim 11 whose 2-tetrahydro furil carboxamide is (2S)-tetrahydro furil carboxamide.
[Claim 13]Bioactive peptide. [Formula 2]



It comes out and is a certain manufacturing method according to claim 1.
[Claim 14]Bioactive peptide.[Formula 3]

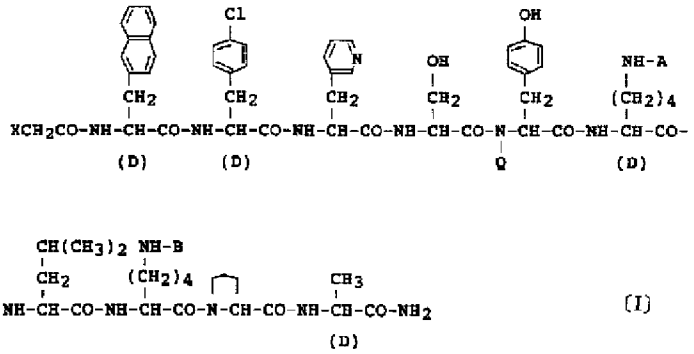


It comes out and is a certain manufacturing method according to claim 1.
[Claim 15]A sustained release drug manufactured by the manufacturing method according to claim 1.
[Claim 16]The sustained release drug according to claim 15 whose content of bioactive peptide is about 0.01 thru/or about 50% (W/W) to biodegradation nature polymer.
[Claim 17]The sustained release drug according to claim 15 which is a microcapsule.
[Claim 18]The sustained release drug according to claim 17 whose microcapsule is an object for injection.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]This invention relates to the manufacturing method of the sustained release drug containing the bioactive peptide which has LH-RH antagonism,

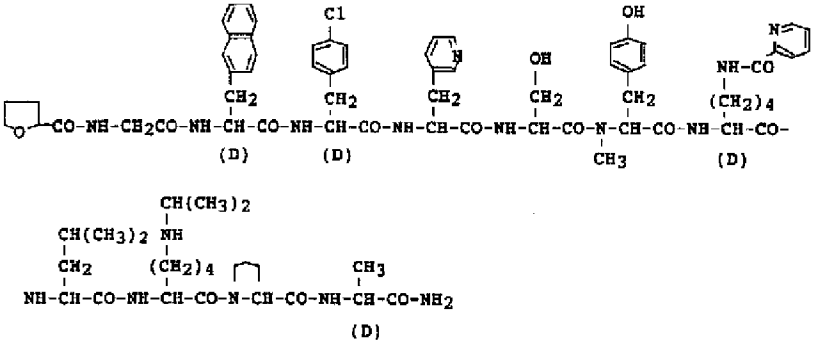
or its salt.
[0002]
[Description of the Prior Art]As a Prior art, for example to EP-A-601,799. Bioactive peptide and the biodegradation nature polymer which has a carboxyl group of isolation at the end are once dissolved in the solvent which is not substantially mixed with water, and the process (an underwater dry technique, a phase separation method, spray drying process using an O/W emulsion) of the sustained release drug by subsequently removing a solvent is indicated.
[0003]
[Problem(s) to be Solved by the Invention]although the histamine isolation operation was a problem in the LH-RH (luteinizing hormone releasing hormone) antagonist called the 1st generation or the second generation (monthly drug regulatory affairs.) Many compounds are compounded after that and the bioactive peptide (for example, refer to JP,3-101695,A) which has the LH-RH antagonism from which a histamine isolation operation does not pose a problem is appearing in 32 volumes, 1599-1605 pages, and 1990. In order for the bioactive peptide which has such LH-RH antagonism to demonstrate drug effect, there is the necessity of always checking an operation of LH-RH in the living body competitively, and it looks forward to these sustained release drugs. And although it is small, the method of manufacturing the sustained release drug in which an excessive amount of drug release especially immediately after administration was controlled is called for for the histamine isolation operation which is not. In [for a long period of time (for example, 1 thru/or 3 months)] a mold sustained release drug, In order to acquire a safe and more positive effect, discharge of steady bioactive peptide with higher certainty is important SUBJECT, bioactive peptide is emitted regularly and the manufacturing method of the sustained release drug which has the preservation stability outstanding moreover is called for.
[0004]
[Means for Solving the Problem]This invention is (1) type. [Formula 4]



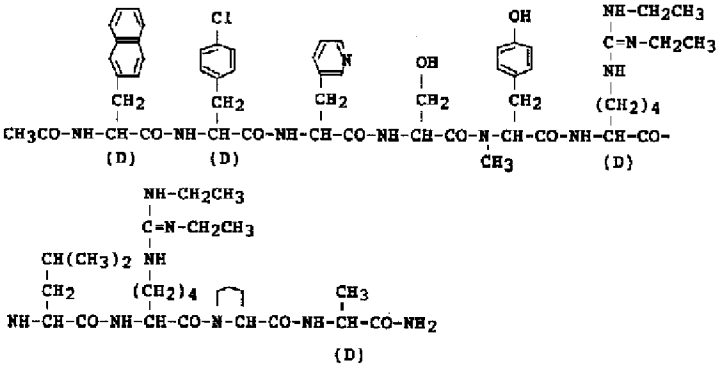
(I)

[Q among a formula hydrogen or tetrahydro furil carboxamide X hydrogen or methyl, The liquid containing the bioactive peptide expressed with A showing nicotinoyl or N,N'-diethyl amidino, and B showing isopropyl or N,N'-diethyl amidino] or its salt is made into the inner aqueous phase, The W/O type emulsified matter which makes an oil phase the solution containing the biodegradation nature polymer which has a carboxyl group of isolation at the end is manufactured, Subsequently, a manufacturing method of the sustained release drug adding the emulsified matter obtained to an outer water phase, and manufacturing a W/O/W type emulsified matter, (2) A manufacturing method of the aforementioned (1) statement whose biodegradation nature polymer is aliphatic polyester, (3) A manufacturing method of the aforementioned (2) statement whose aliphatic polyester is a lactic acid-glycolic acid copolymer, (4) A manufacturing method of the aforementioned (3) statement whose composition ratios (mol %) of lactic acid of

a lactic acid-glycolic acid copolymer and glycolic acid are about 100/0 thru/or about 40/60, (5) A manufacturing method of the aforementioned (3) statement whose weight average molecular weight of a lactic acid-glycolic acid copolymer is about 5,000 thru/or about 20,000, a manufacturing method of the aforementioned (1) statement whose concentration of bioactive peptide in (6) inner aqueous phase is about 0.1 thru/or about 150% (W/V). (7) A manufacturing method of the aforementioned (1) statement whose concentration of biodegradation nature polymer in an oil phase is about 0.1 thru/or about 80% (W/W), (8) A manufacturing method of the aforementioned (1) statement whose quantitative ratios of the inner aqueous phase to an oil phase are about 1 thru/or about 50% (V/V), (9) A manufacturing method of the aforementioned (1) statement it is about 1 of oil phase volume thru/or about 10,000 times whose volume of an outer water phase of this, (10) A manufacturing method of the aforementioned (1) statement whose sustained release drug is a microcapsule, (11) In (12) 2-tetrahydro furil carboxamide, the manufacturing method of the aforementioned (1) statement whose X is 2-tetrahydro furil carboxamide, the manufacturing method of the aforementioned (11) statement which is (2S)-tetrahydro furil carboxamide, and (13) bioactive peptide. [Formula 5]



It comes out and a manufacturing method given in aforementioned [a certain] (1) and (14) bioactive peptide.[Formula 6]



The sustained release drug which comes out and is manufactured by the manufacturing method given in aforementioned [a certain] (1), and a manufacturing method given in (15) aforementioned (1), (16) The sustained release drug of the aforementioned (15) statement whose content of bioactive peptide is about 0.01 thru/or about 50% (W/W) to biodegradation nature polymer, (17) The sustained release drug of the aforementioned (15) statement which is a microcapsule, and (18) microcapsules are related with the sustained release drug of the aforementioned (17) statement which is an object for injection.

[0005]The cable address used in this specification shows the following meanings.

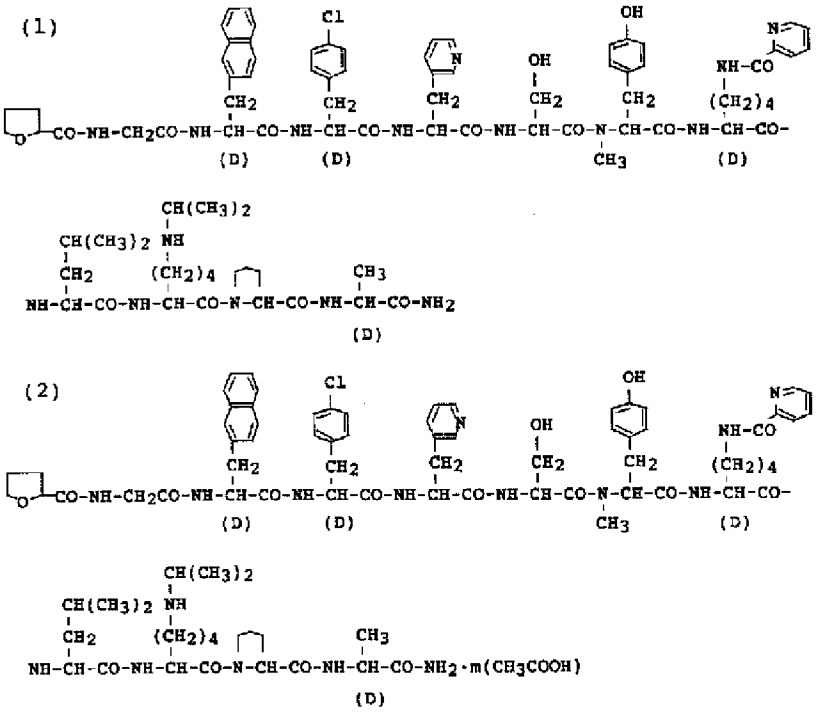
NAcD2Nal. : N-acetyl-D-3-. (2-naphthyl) Alanyl D4ClPhe. : D-3-(4-chlorophenyl) alanyl D3P al. : The D-3-(3-pyridyl) alanyl NMeTyr. N-methyltyrosyl DLys(Nic):D-(epsilon delta technique N-nicotinoyl) lysyl Lys(Nisp) : (epsilon delta technique N-isopropyl) : About lysyl DhArg(Et_2):D-(N,N'-diethyl) gay arginyl and other amino acid, When displaying by a cable address, IUPAC-IUB commission OBU biochemical nomen clay CHUA (Commission on BiochemicalNomenclature) (European journal OBU biochemistry .) (European Journal of Biochemistry) Especially when there may be an optical isomer based on the cable address by the 138th volume, 9-37 pages, and 1984, or the conventional cable address in an applicable field, L object shall be shown if not shown clearly.

[0006]In this invention, it is a formula. [I] Bioactive peptide expressed (the following, peptide) [I]May carry out abbreviated or the salt has LH-RH antagonism, A prostatic cancer, prostatomegaly, endometriosis, fibroid, metrofibroma, pubertas praecox, a breast cancer, vesical cancer, a carcinoma of uterine cervix, chronic lymphatic leukemia, chronic myelogenous leukemia, colon cancer, gastritis, Hodgkin's disease, a malignant melanoma, metastasis, a multiple myeloma, a non-HOJIKIN nature lymphoma, non-small cell lung cancer, an ovarian cancer, a peptic ulcer, a systemic mycosis, small cell lung cancer, a cardiac valvular disease, a mastopathy, a polycystic ovary, sterility, fitness induction of ovulation in a chronic anovulation woman, and ** -- right [that] (acne), Amenorrhea (an example, secondary amenorrhea), the ovary, and a cystic disease of an udder (a polycystic ovary is included), It is effective in a therapy of hormonal dependence diseases, such as male contraception for a therapy of cancer of a gynecology system, ovarian high androgen **** and a virilism, AIDS by T cell production through thymus gland blastogenesis, and a masculinity offender, and contraception, decrudescence of premenstrual syndrome (PMS), in vitro fertilization (IVF), etc.

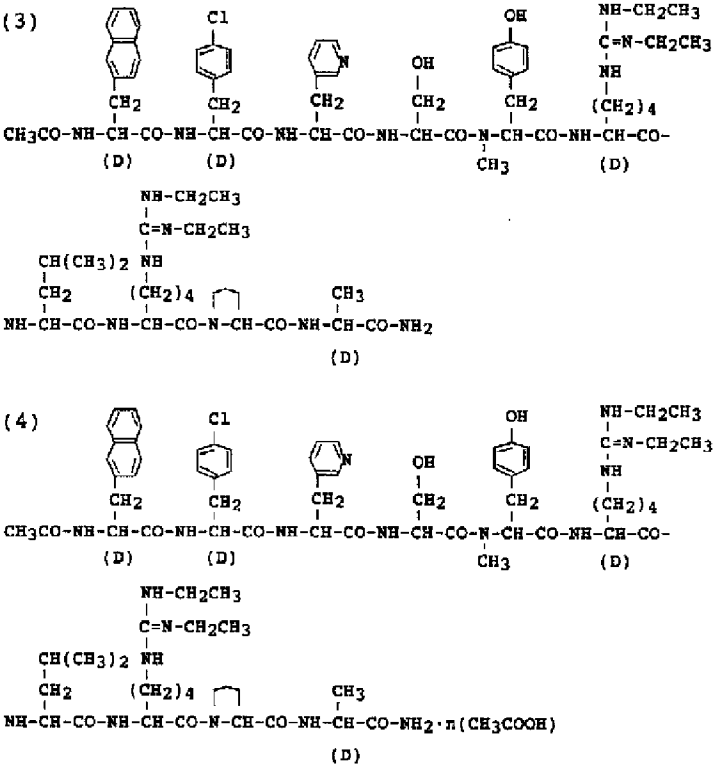
[0007]Formula[I] Setting, X is 2-tetrahydro furil carboxamide preferably. X is - (2S) tetrahydro furil carboxamide still more preferably. A is nicotinoyl preferably. B is isopropyl preferably. Peptide[I] When it has one or more sorts of asymmetric carbon atoms, two or more sorts of optical isomers exist. Such optical isomers and these mixtures are also contained in this invention.

[0008]Peptide[I]or the salt -- the very thing -- it can manufacture by a publicly known method. As such a method, for example JP,3-101695,A, Journal of Medicinal Chemistry (Journal of Medicinal Chemistry), A method similar to a method of a statement or this is mentioned to 35 volumes, 3942 pages (1992), etc. Peptide[I] A salt permitted pharmacologically preferably is used as a salt. As such a salt, a salt with inorganic acid (an example, chloride, sulfuric acid, nitric acid, etc.), organic acid (an example, carbonic acid, GCC acid, succinic acid, acetic acid, propionic acid, trifluoroacetic acid, etc.), etc. is mentioned. Peptide[I] A salt is a salt with organic acid (an example, carbonic acid, GCC acid, succinic acid, acetic acid, propionic acid, trifluoroacetic acid, etc.) still more preferably. Peptide[I] A salt is a salt with acetic acid especially preferably. These salts may be any of MONO thru/or the Tori salt. Preferably, they are JI thru/or the Tori salt.

[0009]Peptide[I]Or a desirable example of the salt is shown below.
[Formula 7]



[m shows the real number of 1 thru/or 3 among a formula.]
[Formula 8]



[n shows the real number of 1 thru/or 3 among a formula.]
Peptide[I]Or the salt is the above (1) and (2) especially preferably.
[0010]The biodegradation nature polymer which has a carboxyl group of isolation at the end is biodegradation nature polymer the number average molecular weight by GPC measurement and whose number average molecular weight by the end group determination correspond mostly. The number average molecular weight by the end group determination is computed as follows. About 1 thru/or 3 g of biodegradation nature polymer are dissolved in the mixed solvent of acetone (25 ml) and methanol (5 ml), The carboxyl group in this solution is promptly titrated by using phenolphthalein as an indicator with a bottom of churning 0.05N alcoholic pottasium hydroxide solution in a room temperature (20 **), and a number average molecular weight is computed from a following formula.
Number-average-molecular-weight =20000xA/BA by the end group determination:
Mass (g) of biodegradation nature polymer
B: Quantity of a 0.05N alcoholic pottasium hydroxide solution added even to a titration end point (ml)
For example, it is compounded by a non-catalyst dehydration polycondensation method from one or more kinds of alpha-hydroxy acids, and a number average molecular weight by GPC measurement and a number average molecular weight by an end fixed quantity are mostly in agreement in a polymer which has a carboxyl group of isolation at the end. On the other hand, it is compounded by a ring-opening-polymerization method using a catalyst from a cyclic dimer, and a number average molecular weight by the end group determination far exceeds a number average molecular weight by GPC measurement in a polymer which does not have a carboxyl group of isolation substantially at the end. A polymer which has a carboxyl group of isolation at the end according to this difference is clearly distinguishable from a polymer which does not have a carboxyl group of isolation at the end.
[0011]A number average molecular weight according to GPC measurement to a number average molecular weight by the end group determination being an absolute value is a relative value changed with various analysis and analysis conditions (for example, selection of a kind of mobile phase, a kind of column, a primary standard, and slice width, selection of a baseline, etc.). Therefore, although correlation by both most important numerical value is difficult, for example, that a number average molecular weight by GPC measurement and a number average molecular weight by the end group determination are mostly in agreement, A number average molecular weight by the end group determination says that they are about 1.5 times [about 0.8 to] as many ranges still more preferably twice [about] from about 0.5 time preferably twice [about] from about 0.4 time of a number average molecular weight by GPC measurement. That a number average molecular weight by the end group determination far exceeds a number average molecular weight by GPC measurement means that a number average molecular weight by the end group determination exceeds the twice [about] of a number average molecular weight by GPC measurement.
[0012]As an example of biodegradation nature polymer of having a carboxyl group of isolation at the end, For example, alpha-hydroxycarboxylic acid (an example, glycolic acid, lactic acid, hydroxybutyric acid, etc.). hydroxydicarboxylic acid and hydroxy tricarboxylic acid (an example, malic acid, etc.) (an example.) A polymer compounded by non-catalyst dehydration polycondensation from one or more sorts, such as citrate Hitoshi, Copolymers or these mixtures, Polly alpha-cyanoacrylic ester, polyamino acid, maleic anhydride (example, Polly gamma-benzyl-L-glutamic acid, etc.) system copolymers (an example, a styrene maleic acid copolymer, etc.), etc. are mentioned. biodegradation nature polymer -- desirable -- aliphatic polyester (an example.), for example, alpha-hydroxycarboxylic acid A polymer compounded by non-catalyst dehydration polycondensation from one or more sorts, such as hydroxydicarboxylic acid,

hydroxy tricarboxylic acid (an example, malic acid, etc.), etc. (an example, citrate, etc.), such as glycolic acid, lactic acid, and hydroxybutyric acid, copolymers, or these mixtures are mentioned. Any of randomness, a block, and a graft may be sufficient as form of a polymerization. When above-mentioned alpha-hydroxy acids, hydroxydicarboxylic acid, and hydroxy tricarboxylic acid have an optical activity center in intramolecular, both D- L- and DL-object can be used.

[0013]biodegradation nature polymer which has a carboxyl group of isolation at the end -- desirable -- a (1) lactic-acid-glycolic acid copolymer or (2) and (A) glycolic acid, and a formula [Formula 9]

It is the biodegradation nature polymer which mixed a copolymer with the hydroxycarboxylic acid shown by (R expresses the alkyl group of the carbon numbers 2-8 among a formula), and (B) polylactic acid. The biodegradation nature polymer which has a carboxyl group of isolation at the end is a lactic acid-glycolic acid copolymer especially preferably.

[0014]When using a lactic acid-glycolic acid copolymer as biodegradation nature polymer, the composition ratio (lactic acid/glycolic acid) (mol %) does not have about 100/0, and 60 is preferred about 40/. Composition ratios are about 90/10 thru/or about 50/50 still more preferably. The weight average molecular weight of the above-mentioned lactic acid-glycolic acid copolymer is about 5,000 to about 25,000 preferably. weight average molecular weight -- further -- desirable -- about 7,000 to about 20,000 -- it is about 8,000 to about 15,000 especially preferably. The degree of dispersion (weight average molecular weight/number average molecular weight) of a lactic acid-glycolic acid copolymer is about 1.2 to about 4.0 preferably. A degree of dispersion is about 1.5 to about 3.5 still more preferably. The above-mentioned lactic acid-glycolic acid copolymer can be manufactured in accordance with a publicly known manufacturing method, for example, a manufacturing method given in JP,61-28521,A.

[0015]Although decomposition / disappearance speed of a lactic acid-glycolic acid copolymer changes with a presentation or molecular weights a lot, since decomposition and disappearance are slow, it can lengthen a release period by making a glycolic acid molar fraction low, or enlarging a molecular weight, so that a glycolic acid molar fraction is generally low. On the contrary, a release period can also be shortened by making a glycolic acid molar fraction high, or making a molecular weight small. In order to consider it as a mold sustained release drug for a long period of time (for example, 1 thru/or 4 months), a lactic acid-glycolic acid copolymer of the above-mentioned composition ratio and the range of weight average molecular weight is preferred. If a lactic acid-glycolic acid copolymer in which decomposition is quicker than a lactic acid-glycolic acid copolymer of the above-mentioned composition ratio and the range of weight average molecular weight is chosen, control of an initial burst is difficult, Conversely, if a lactic acid-glycolic acid copolymer in which decomposition is slower than a lactic acid-glycolic acid copolymer of the above-mentioned composition ratio and the range of weight average molecular weight is chosen, it will be easy to produce a period when an effective dose of drugs are not emitted.

[0016]The above-mentioned formula [II]As an alkyl group of a straight chain of the carbon numbers 2-8 shown by R inside, or a letter of branching, For example, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl one, tert-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, etc. are mentioned. Preferably, an alkyl group of a straight chain of the carbon numbers 2-5 or a letter of branching is used. As an example, ethyl, propyl, isopropyl, butyl, isobutyl, etc. are mentioned, for example. R is ethyl

especially preferably.
[0017]Formula[II] As hydroxycarboxylic acid shown, 2-hydroxybutyric acid, 2-hydroxyvaleric acid, 2-hydroxy-3-methylbutyric acid, 2-hydroxycaproic acid, 2-hydroxyisocaproic acid, 2-hydroxycapric acid, etc. are mentioned, for example. Among these [especially], 2-hydroxybutyric acid, 2-hydroxyvaleric acid, 2-hydroxy-3-methylbutyric acid, and 2-hydroxycaproic acid are preferred. Formula[II] Hydroxycarboxylic acid shown is 2-hydroxybutyric acid especially preferably. Although any of D-object, L-object and D, and L-object may be sufficient as these hydroxycarboxylic acid, D-object / L-object (mol %) does not have about 75/25, and its thing of the range of 75 is preferred about 25/. Still more preferably, D-object / L-object (mol %) does not have about 60/40, and is hydroxycarboxylic acid of the range of 60 about 40/. Especially preferably, D-object / L-object (mol %) does not have about 55/45, and is hydroxycarboxylic acid of the range of 55 about 45/.
[0018]Glycolic acid and a formula [II] In a copolymer (it is hereafter called a glycolic acid copolymer (A) for short) with hydroxycarboxylic acid shown, any of randomness, a block, and a graft may be sufficient as form of copolymerization. Preferably, it is a random copolymer. Formula[II] Hydroxycarboxylic acid shown may be used at one sort or a rate proper two or more sorts. Glycolic acid and a formula in a glycolic acid copolymer (A) [II] Composition ratio with hydroxycarboxylic acid shown has a preferred case where glycolic acid is % and about 10 thru/or the about 75-mol remainder are hydroxycarboxylic acid. It is a case where glycolic acid is about 20 thru/or about 75-mol %, and the remainder is hydroxycarboxylic acid, still more preferably. It is a case where glycolic acid is about 40 thru/or about 70-mol %, and the remainder is hydroxycarboxylic acid, especially preferably. As for these glycolic acid copolymers, about 2,000 to about 50,000 thing is used for weight average molecular weight. Weight average molecular weight is about 3,000 to about 40,000 preferably. Weight average molecular weight is about 8,000 to about 30,000 still more preferably. A degree of dispersion (weight average molecular weight/number average molecular weight) of these glycolic acid copolymers is about 1.2 to about 4.0 preferably. A degree of dispersion is about 1.5 to about 3.5 especially preferably. The above-mentioned glycolic acid copolymer (A) can be manufactured in accordance with a publicly known manufacturing method, for example, a method given in JP,61-28521,A.
[0019]As polylactic acid, although any of L-object, D-objects, and these mixtures may be sufficient, D-object / L-object (mol %) does not have about 75/25, and a thing of the range of 80 is preferred about 20/. Still more preferably, D-object / L-object (mol %) does not have about 60/40, and is polylactic acid of the range of 75 about 25/. Especially preferably, D-object / L-object (mol %) does not have about 55/45, and is polylactic acid of the range of 75 about 25/. Weight average molecular weight of this polylactic acid is about 1,500 to about 30,000 preferably. Weight average molecular weight is about 2,000 to about 20,000 still more preferably. Weight average molecular weight is about 3,000 to about 15,000 especially preferably. A degree of dispersion of polylactic acid is about 1.2 to about 4.0 preferably. A degree of dispersion is about 1.5 to about 3.5 especially preferably. About a manufacturing method of polylactic acid, a method of carrying out ring opening polymerization of RAKUCHIDDO which is a dimer of lactic acid, and a method of carrying out dehydration polycondensation of the lactic acid are known. In order [which is used by this invention] to obtain polylactic acid of low molecular weight comparatively, a method of carrying out dehydration polycondensation of the lactic acid directly is preferred. This manufacturing method is indicated, for example to JP,61-28521,A.
[0020]The mixture ratio (% of the weight) expressed with (A)/(B), for example does not have about 10/90, and a glycolic acid copolymer (A) and about 90/of polylactic acid (B) are used in 10. The mixture ratio (% of the weight) is about 20/80 thru/or about 80/20 preferably. The mixture ratio (% of the weight) is about 30/70 thru/or about 70/30 still more preferably. If there are too many which ingredients among (A) and (B), only

pharmaceutical preparation which has the almost same drug release pattern as a case where (A) or the (B) ingredient is used alone will be obtained, and a linear discharge pattern in the second half of discharge by a mixed base agent cannot be expected. Although decomposition / disappearance speed of a glycolic acid copolymer (A) and polylactic acid changes with a molecular weight or presentations a lot, Generally, since the decomposition / disappearance speed of a glycolic acid copolymer (A) is quicker, a release period can be lengthened by making small the mixture ratio which enlarges a molecular weight of polylactic acid to mix, or is expressed with (A)/(B). On the contrary, a release period can also be shortened by enlarging the mixture ratio which makes a molecular weight of polylactic acid to mix small, or is expressed with (A)/(B). Formula[II] A release period can also be adjusted by changing a kind and a rate of hydroxycarboxylic acid which are shown.

[0021]With weight average molecular weight in this specification, and a degree of dispersion. Polystyrene whose weight average molecular weight is nine kinds, 120,000, 52,000, 22,000, 9,200, 5,050, 2,950, 1,050, 580, and 162, is used as a primary standard. A molecular weight and a computed degree of dispersion of polystyrene conversion measured with gel permeation chromatography (GPC) are said. Measurement used chloroform for GPC column KF804Lx2 (made by Showa Denko), and the RI monitor L-3300 (made by Hitachi) as use and a mobile phase.

[0022]Below, a manufacturing method of this invention is explained in full detail. First, peptide [I]Or the salt (it may carry out abbreviated to a drug hereafter) is dissolved or distributed in water, and if required for this, drug maintenance substances, such as gelatin, agar, poly vinyl alcohol, or basic amino acid (for example, arginine, histidine, lysine), will be added, and it will be dissolved or suspended, and will be considered as inner aqueous phase. Concentration of a drug in inner aqueous phase is about 0.1 thru/or about 150% (W/V) preferably. They are about 20 thru/or about 130% (W/V) still more preferably. They are about 60 thru/or about 120% (W/V) especially preferably. In inner aqueous phase, carbonic acid, acetic acid, oxalic acid, citrate, phosphoric acid, chloride, etc. may add sodium hydroxide, arginine, lysine, those salts, etc. as a pH adjuster for maintaining the stability of a drug, and solubility. As a stabilizing agent of a drug, albumin, gelatin, citrate, As polyol compounds, such as sodium ethylenediaminetetraacetate, dextrin, sodium hydrogen sulfite, and a polyethylene glycol, or a preservative, P-hydroxybenzoate esters (methylparaben, propylparaben, etc.), benzyl alcohol, chlorobutanol, a thimerosal, etc. which are generally used may be added.

[0023]Thus, it adds into a solution (oil phase) containing biodegradation nature polymer (it may carry out abbreviated to polymer hereafter) which has a carboxyl group of isolation of obtained inner aqueous phase at the end, subsequently emulsification operation is performed, and a W/O type emulsified matter is manufactured. This emulsification operation is performed by method by mixers, such as a publicly known dispersion method, for example, intermittence vibration, a propeller type agitator, or a turbine type agitator, the colloid mill method, the homogenizer method, an ultrasonic irradiation method, etc. That by which a solution (oil phase) containing the above-mentioned polymer dissolved this polymer in an organic solvent which is not substantially mixed with water is used. Solubility to water of this organic solvent is below 3% (W/W) at ordinary temperature (20 **) preferably. As for the boiling point of an organic solvent, it is preferred that it is 120 ** or less. As an organic solvent, for example Halogenated hydrocarbon (an example, dichloromethane, chloroform, chloroethane, trichloroethane, carbon tetrachloride, etc.), With a carbon numbers of three or more alkyl ether, alkyl (four or more carbon numbers) ester (an example, butyl acetate, etc.) of fatty acid (an example, isopropyl ether, etc.), aromatic hydrocarbon (an example, benzene, toluene, xylene, etc.), etc. are mentioned. These may be mixed and used at a rate proper two or more sorts. Organic solvents are halogenated hydrocarbon (an example, dichloromethane, chloroform, chloroethane, trichloroethane, a carbon

tetrachloride, etc.) still more preferably. An organic solvent is dichloromethane especially preferably. Although concentration of polymer in an oil phase changes with a molecular weight of this polymer, and kinds of solvent, it is about 0.01 thru/or about 80% (W/W) preferably. They are about 0.1 thru/or about 70% (W/W) still more preferably. They are about 1 thru/or about 60% (W/W) especially preferably. In a sustained release drug, although loadings of a drug change with duration of a kind of drug, a desired medicinal value, and an effect, etc., they are used from about 0.01 about 50% (w/w) to biodegradation nature polymer of a base. Preferably, it is used about 40% (w/w) from about 0.1. It is especially used about 30% (w/w) from about 1 preferably.

[0024]Subsequently, a W/O type emulsified matter manufactured by doing in this way is given to an underwater dry technique. This underwater dry technique is performed by removing a solvent in an oil phase, after adding a W/O type emulsified matter into aqueous phase (outer water phase) and making a W/O/W type emulsified matter form. Volume of an outer water phase is generally chosen from about 1 of oil phase volume thru/or about 10,000 times. It is chosen out of about 2 thru/or about 5,000 times still more preferably. It is especially chosen out of about 5 thru/or about 2,000 times preferably. An emulsifier may be added into the above-mentioned outer water phase. As long as this emulsifier can generally form a stable W/O/W type emulsified matter, any may be sufficient as it. Specifically, they are anionic surface-active agents (sodium oleate, sodium stearate, sodium lauryl sulfate, etc.) and a nonionic surfactant (polyoxyethylene sorbitan fatty acid ester), for example. [Tween (Tween)80, Tween (Tween)60, an atlas powder company] Polyoxyethylene-castor-oil derivative [HCO-60, HCO-50, Nikko Chemicals] ****, a polyvinyl pyrrolidone, polyvinyl alcohol, carboxymethyl cellulose, lecithin, gelatin, hyaluronic acid, etc. are mentioned. An emulsifier is polyvinyl alcohol preferably. It may be used combining one kind and some in these emulsifiers. Concentration in the case of use can be suitably chosen from about 0.001 to about 20% (W/W) of range. It is used in about 0.01 to about 10% (W/W) of range still more preferably. It is especially used in about 0.05 to about 5% (W/W) of range preferably.

[0025]An osmoregulating chemical may be applied into the above-mentioned outer water phase. When it is considered as solution as an osmoregulating chemical used by this invention, as long as osmotic pressure is shown, it may be what kind of substance. As an example of this osmoregulating chemical, water-soluble polyhydric alcohol class, water-soluble monohydric alcohol, water-soluble monosaccharide, disaccharide and oligosaccharide or those derivatives, water-soluble amino acid, water-soluble peptide, protein, or those derivatives etc. are mentioned, for example.

[0026]As the water-soluble above-mentioned polyhydric alcohol class, hexahydric alcohol, such as pentavalent alcohols, such as dihydric alcohol, such as glycerin, arabitol, xylitol, and adonitol, mannitol, sorbitol, and dulcitol, is mentioned, for example. Alcohols of 6 values are [among these] preferred. Especially, especially mannitol is preferred. As the water-soluble above-mentioned monohydric alcohol, methanol, ethanol, isopropyl alcohol, etc. are mentioned, for example. Ethanol is [among these] preferred. As the water-soluble above-mentioned monosaccharide, hexose, such as pentose, such as arabinose, xylose, and ribose .2-deoxyribose, grape sugar, fructose, galactose, mannose, a sorbose, rhamnose, and fucose, is mentioned, for example. Hexose is [among these] preferred. As the water-soluble above-mentioned disaccharide, maltose, cellobiose, alpha, and alpha-trehalose, milk sugar, sucrose, etc. are mentioned, for example. Milk sugar and sucrose are [among these] preferred. As the water-soluble above-mentioned oligosaccharide, tetrasaccharides, such as trisaccharides, such as a maltotriose and raffinose, and a stachyose, etc. are mentioned, for example. Trisaccharide is [among these] preferred. As a derivative of the water-soluble above-mentioned monosaccharide, disaccharide, and oligosaccharide, glucosamine, galactosamine, glucuronic acid, galacturonic acid, etc. are mentioned, for example.

[0027]As amino acid of the above-mentioned solution, for example Neutral amino acid, such as a glycine, an alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, proline, hydroxyproline, cystein, and methionine, an iron permanent wave -- basic amino acid, such as acidic amino acid, such as RAGIN acid and glutamic acid, lysine, arginine, and histidine, etc. are mentioned. Acid (an example, chloride, sulfuric acid, phosphoric acid, etc.) of these water-soluble amino acid or a salt with alkali (alkaline metals, such as an example, sodium, and potassium etc.) may be used. As water-soluble peptide, protein, or those derivatives, casein, globulin, prolamin, albumin, gelatin, etc. are mentioned, for example. Water-soluble polyhydric alcohol class and water-soluble monosaccharide, disaccharide and oligosaccharide, or those derivatives are preferred among the above-mentioned osmoregulating chemicals. A water-soluble polyhydric alcohol class and water-soluble monosaccharide are still more preferred. It is a water-soluble, especially desirable polyhydric alcohol class. These osmoregulating chemicals may be used alone, or may mix and use one or more sorts. As for these osmoregulating chemicals, osmotic pressure of an outer water phase is used by about 1/50 of osmotic pressure of a physiological saline thru/or concentration which will be about 1/25 thru/or about 3 times preferably about 5 times. Specifically concentration in inside of an outer water phase of these osmoregulating chemicals, a case where an osmoregulating chemical is a nonionic substance -- about 0.001% thru/or about 60% (W/W) -- desirable -- about 0.01% thru/or about 40% (W/W) -- more -- desirable -- about 0.05% -- or they are about 1% thru/or about 10% (W/W) especially preferably about 30% (W/W). When an osmoregulating chemical is an ionic substance, concentration which **(ed) the above-mentioned concentration by the whole ionic valency is used. The addition concentration of an osmoregulating chemical does not need to be below solubility, and a part may be a dispersion state.

[0028]In a manufacturing method of this invention, when making a W/O/W type emulsified matter form, it is preferred to adjust viscosity of a W/O type emulsified matter to about 150 cp thru/or about 10,000 cp. . As a method of adjusting viscosity, adjust concentration of biodegradation nature polymer of (1) oil phase, for example. (2). Adjust temperature of (3) W/O type emulsified matter which adjusts a quantitative ratio of aqueous phase and an oil phase. (4) When pouring into an outer water phase (5) W/O type emulsified matter which adjusts temperature of an outer water phase, these methods may be independent, or a method of adjusting temperature of a W/O type emulsified matter with a line heater, an air conditioner, etc., for example may be mentioned, and they may be used, combining. In short in a described method, viscosity of a W/O type emulsified matter in case a W/O type emulsified matter turns into a W/O/W type emulsified matter should just carry out even making it set to about 150 cp thru/or about 10,000 cp. In the above (1), since concentration in a case of adjusting concentration of biodegradation nature polymer of an oil phase changes by kind of biodegradation nature polymer, a kind of organic solvent, etc., it is not determined uniquely, but it is about 10 thru/or about 80% (W/W) preferably. although a quantitative ratio in a case of adjusting a quantitative ratio of aqueous phase and an oil phase is not what is uniquely determined with a kind of drug and quantity, and character of an oil phase in the above (2) -- desirable -- W/O= -- they are about 1% thru/or about 50% (V/V). temperature in a case of adjusting temperature of a W/O type emulsified matter in the above (3) -- about -20 ** thru/or the range of the boiling point of an organic solvent -- desirable -- about 0 ** -- or about 30 ** is about 10 ** thru/or about 20 ** still more preferably. The above (1) and in the case of (2), the stage of adjustment of viscosity of a W/O type emulsified matter can carry out, when manufacturing a W/O type emulsified matter. What is necessary is just to make it bring the same result as the above (3) by adjusting temperature of an outer water phase beforehand in the above (4), when adding a W/O type emulsified matter to an outer water phase. Temperature of an outer water phase does not have about 5 **, does not have preferably about 10 ** of about 30 **, and is about 12 ** thru/or about 20 ** still more preferably about 25 **,

for example.
[0029]a method of removing an organic solvent -- the very thing -- it can carry out in accordance with a publicly known method. For example, a method of evaporating an organic solvent, etc. are mentioned, adjusting a degree of vacuum using ordinary pressure or a method of using decompression gradually and evaporating an organic solvent, a rotating evaporator, etc. agitating with a propeller type agitator or a magnetic stirrer.
[0030]Thus, after centrifuging or ****(ing) and isolating preparatively an obtained sustained release drug, for example, a microcapsule, (called a microsphere), A drug of isolation which has adhered on the surface of a microcapsule, a drug maintenance substance, an emulsifier, etc. are repeated several times, and distilled water washes them, and re dispersion is carried out to distilled water etc., and it freeze-dries. A condensation inhibitor may be added in the case of freeze-drying. As this condensation inhibitor, water-soluble polysaccharides, such as mannitol and starch (an example, cornstarch, etc.), mineral, amino acid, protein, etc. are mentioned, for example. It is mannitol preferably [among these]. the mixture ratio (weight ratio) of a microcapsule and a condensation inhibitor -- about 50:1 thru/or about 1:1 -- desirable -- about 20:1 thru/or about 1:1 -- it is about 10:1 thru/or about 5:1 still more preferably. In order to prevent condensation of the particles under washing, a condensation inhibitor may be added to distilled water which is a penetrant remover. As this condensation inhibitor, mineral, such as protein, such as water-soluble polysaccharides, such as mannitol, lactose, grape sugar, and starch (an example, cornstarch, etc.), a glycine, fibrin, and collagen, sodium chloride, and dibasic sodium phosphate, etc. are mentioned, for example. A condensation inhibitor is mannitol preferably.
[0031]After freeze-drying, by request, it may warm under decompression and moisture in a microcapsule and removal of an organic solvent may be performed further. there is no effect of an excessive amount of initial discharge nature improvements of bioactive peptide at less than glass transition temperature of biodegradation nature polymer which cooking temperature used as a base -- quantity -- if too tepid, danger, such as weld of a microcapsule, modification, disassembly of a physiological active substance, and degradation, will increase. Although cooking temperature cannot generally be said, in consideration of mean particle diameter of the physical properties (an example, a molecular weight, stability, etc.) of biodegradation nature polymer used as a base, bioactive peptide, and a microcapsule, cooking time, a desiccation grade of a microcapsule, a heating method, etc., it can determine suitably. Preferably, it is more than glass transition temperature of biodegradation nature polymer used as a base, and stoving is carried out at temperature of a grade to which each particle of this microcapsule does not adhere mutually. Stoving is more preferably carried out from glass transition temperature of biodegradation nature polymer used as a base in a temperature requirement higher about 30 ** than glass transition temperature. using a differential scanning calorimeter with glass transition temperature in here -- warming -- halfway point glass transition temperature obtained when temperature up is carried out at the speed 10 [per minute] or 20 ** is said. Although stoving time also changes with cooking temperature, amounts of microcapsules to process, etc., after temperature of the microcapsule itself generally reaches a predetermined temperature, about 24 thru/or about 120 hours are preferred. Further about 48 thru/or about 120 hours are preferred. Although a heating method in particular is not limited, as long as a microcapsule is a method heated uniformly, what kind of method may be used. As a desirable example of this stoving method, a method of carrying out stoving, for example in a thermostat, a flow tub, the moving bed, or a kiln, a method of carrying out stoving with microwave, etc. are used. In these, a method of carrying out stoving in a thermostat is preferred. As mentioned above, after freeze-drying, by warming a microcapsule under decompression, an organic solvent in a microcapsule is removed efficiently and a microcapsule safe for a living body can be obtained. Thus, organic solvent ullage in an obtained microcapsule

is about 100 ppm or less.
[0032]It pharmaceutical-preparation-izes to various dosage forms by using to remain as it is or a microcapsule as a source material, and microcapsules are parenterals (passing membrane agent [uterus / injections to an example, intramuscular, hypodermic, an organ, etc. or an embedding agent, a nasal cavity, the rectum,] etc.), and an oral agent. [Liquids and solutions, such as solid preparations, such as an example, a capsule, granules (an example, hard capsules, an elastic capsule, etc.), and powder medicine, syrups, an emulsion, and suspension] etc. A medicine can be prescribed for the patient as ****. For example, in order to make a microcapsule into injections, a microcapsule -- a dispersing agent (an example, Tween 80, HCO-60, and carboxymethyl cellulose (carboxymethylcellulose sodium is included).) Preservatives, such as sodium alginate (an example, methylparaben, propylparaben, etc.), It is considered as mixture with isotonizing agents (an example, sodium chloride, mannitol, sorbitol, grape sugar, etc.) etc., or it distributes with vegetable oil, such as sesame oil and corn oil, and is considered as sustained-release injections which can actually be used as oily suspension. The particle diameter of a microcapsule should just be a range with which it is satisfied of the degree of dispersion and needle penetration nature, when using it, for example as suspension for injection, for example, the range of about 0.1 to about 500 micrometers is mentioned as mean particle diameter. Preferably, it is the particle diameter of the range of about 1 to about 300 micrometers. It is the mean particle diameter of the range of about 2 to about 200 micrometers still more preferably. When a sustained release drug is a microcapsule, the shape turns into the shape of a ball it was suitable for by needle penetration nature by applying an osmoregulating chemical into an outer water phase as mentioned above. In order to use a microcapsule as sterile preparation, a method of making a manufacture whole process sterile, for example, a method of sterilizing by a gamma ray, a method of adding an antiseptic, etc. are mentioned, but it is not limited in particular.
[0033]A sustained release drug of this invention can be safely used to mammalians (an example, Homo sapiens, a cow, a pig, a dog, a cat, a mouse, a rat, a rabbit, etc.) by low toxicity. Doses of a sustained release drug are a kind of drug, a content, dosage forms and temporal duration of drug release, and an object illness. [An example, A prostatic cancer, prostatomegaly, endometriosis, fibroid, metrofibroma, pubertas praecox, a breast cancer, vesical cancer, a carcinoma of uterine cervix, chronic lymphatic leukemia, chronic myelogenous leukemia, colon cancer, gastritis, Hodgkin's disease, a malignant melanoma, metastasis, a multiple myeloma, a non-HOJIKIN nature lymphoma, non-small cell lung cancer, an ovarian cancer, a peptic ulcer, a systemic mycosis, small cell lung cancer, a cardiac valvular disease, a mastopathy, a polycystic ovary, sterility, fitness induction of ovulation in a chronic anovulation woman, and ** -- right [that] (acne), Amenorrhea (an example, secondary amenorrhea), the ovary, and a cystic disease of an udder (a polycystic ovary is included), A therapy of hormonal dependence diseases, such as male contraception for a therapy of cancer of a gynecology system, ovarian high androgen **** and a virilism, AIDS by T cell production through thymus gland blastogenesis, and a masculinity offender, and contraception, decrudescence of premenstrual syndrome (PMS), in vitro fertilization (IVF)], etc. Although it changes variously with target animals etc., what is necessary is just an effective dose of a drug. As a dose per time of a drug, when a sustained release drug is one-month pharmaceutical preparation, for example, it can choose out of the range of about 0.01 mg per adult thru/or about 100 mg/kg weight suitably preferably. It can choose out of the range of about 0.05 mg thru/or about 50 mg/kg weight suitably still more preferably. It can choose out of the range of about 0.1 mg thru/or about 10 mg/kg weight suitably preferably especially. A dose of a sustained release drug per time can be preferably chosen from the range of about 0.1 mg thru/or about 500 mg/kg weight suitably per adult. It can choose out of the range of about 0.2 mg thru/or about 300 mg/kg weight suitably still more preferably. Frequency of administration can be chosen by 1 time in 1

time and one month, and can choose it in several months suitably at several weeks by a kind of drugs, such as 1 etc. time, a content, dosage forms and temporal duration of drug release, an object illness, a target animal, etc.

[0034]

[Embodiment of the Invention]A reference example and an example are given to below, and this invention is explained to it still more concretely. Among the following reference examples and an example, % shows weight %, unless it mentions specially.

[Example]

Example 1N-. (S) Acetate of-2-Tetrahydrofuroyl-Gly-D2 Nal-D4 ClPhe-D3Pal-Ser-NMeTyr-DLys(Nic)-Leu-Lys(Nisp)-Pro-DAlaNH$_2$ (it is written as the peptide A below). (Made by TAP) About 500 mg, it is distilled water. It dissolved in 0.6 ml. the solution obtained -- a lactic acid-glycolic acid copolymer (it is hereafter written as PLGA) (the Wako Pure Chem make.) lot.940810, lactic acid/glycolic acid (mole ratio) : Number average molecular weight:3,700 4.5g by 74/26, GPC weight-average-molecular-weight:10,000, GPC number average molecular weight:3,900, and end group analysis is added to the solution which dissolved in 5.8 ml of dichloromethane, It mixed for 60 seconds with the small homogenizer (made by KINEMACHIKA), and the W/O type emulsified matter was obtained. After cooling this W/O type emulsified matter at 16 **, it poured in into 1000 ml of 0.1% polyvinyl alcohol (EG-40, product made from Japanese synthetic chemistry) solution beforehand cooled at 16 **, and was considered as the W/O/W type emulsified matter by 7000 rpm using the turbine type homomixer (product made from the formation of a special opportunity). After having agitated this W/O/W type emulsified matter at the room temperature for 3 hours, vaporizing dichloromethane and solidifying a W/O type emulsified matter, it centrifuged by 2000 rpm using the centrifuge (05PR-22, Hitachi). Dispersion liquid were further centrifuged for the sediment obtained after re dispersion to distilled water, and washing removal of the releaser thing was carried out. The obtained microcapsule was added to a little distilled water, 0.3 g of D-mannitol was added to dispersion liquid after re dispersion, it freeze-dried and the microcapsule was obtained as powder. The content of the particle size distribution of a microcapsule and the peptide A in a microcapsule was 5 thru/or 60 mum, and 9.5% (w/w), respectively.

[0035]example 2PLGA (the Wako Pure Chem make.) lot.940813, lactic acid/glycolic acid (mole ratio): The microcapsule was obtained like Example 1 except using 73/27, GPC weight-average-molecular-weight:13,000, GPC number average molecular weight:4,500, and number average molecular weight:4,700 by end group analysis. The content of the peptide A in 5 thru/or 60 mum, and a microcapsule of the particle size distribution of the microcapsule was 9.5% (w/w).

[0036]example 3P LGA (the Wako Pure Chem make.) lot.940808, lactic acid/glycolic acid (mole ratio): The microcapsule was obtained like Example 1 except using 74/26, GPC weight-average-molecular-weight:7,800, GPC number average molecular weight:3,500, and number average molecular weight:3,000 by end group analysis. The content of the peptide A in 5 thru/or 60 mum, and a microcapsule of the particle size distribution of the microcapsule was 9.5% (w/w).

[0037]The microcapsule was obtained like Example 1 except the quantity of acetate of the example 4 peptide A being 794 mg. The content of the peptide A in 5 thru/or 60 mum, and a microcapsule of the particle size distribution of the microcapsule was 14.3% (w/w).

[0038]About 15 g of acetate of the example 5 peptide A, it is distilled water. It dissolved in 18 ml. the solution obtained -- PLGA (the Wako Pure Chem make.) lot.940810, lactic acid/glycolic acid (mole ratio) : Number average molecular weight:3,700 135g by 74/26, GPC weight-average-molecular-weight:10,000, GPC number average molecular weight:3,900, and end group analysis is added to the solution which dissolved in 174 ml of dichloromethane, It mixed with the homogenizer and the W/O type emulsified matter was obtained. This W/O type emulsified matter was poured

in into 0.1% polyvinyl alcohol (EG-40, product made from Japanese synthetic chemistry) solution 30 l beforehand cooled at 17 **, and was used as the W/O/W type emulsified matter using the inline-type homomixer. After having agitated this W/O/W type emulsified matter at the room temperature, vaporizing dichloromethane and solidifying a W/O type emulsified matter, it centrifuged using the centrifuge. Distilled water washed the sediment obtained and the releaser thing was removed. The obtained microcapsule was added to a little distilled water, 13.5 g of D-mannitol was added to dispersion liquid after re dispersion, and it freeze-dried, and also succeedingly, reduced pressure drying was carried out for 48 hours, and 40 thru/or 43 ** of thermostat Naka obtained 42 thru/or 44 ** of microcapsules as powder for 19 hours. The content of the peptide A in 3 thru/or 60 micrometers and a microcapsule of the particle size distribution of the microcapsule was 8.7% (w/w).

[0039]Instead of acetate of the example 6 peptide A . It is made to be the same as that of Example 1 except using acetate (made by SHINTEKKUSU (Syntex)) of NAcD2 Nal-D4 ClPhe-D3Pal-Ser-Tyr-DhArg(Et_2)-Leu-hArg(Et_2)-Pro-DAlaNH_2. The microcapsule was obtained. The content of peptide in 5 thru/or 60 mum, and a microcapsule of the particle size distribution of the microcapsule was 9.4% (w/w).

[0040]About 857 mg of acetate of the example 7 peptide A, it is distilled water. It dissolved in 0.8 ml. the solution obtained -- PLGA (the Wako Pure Chem make.) lot.950526, lactic acid/glycolic acid (mole ratio) : Number average molecular weight:3,800 4.5g by 74/26, GPC weight-average-molecular-weight:11,700, GPC number average molecular weight:5,200, and end group analysis is added to the solution which dissolved in 6 ml of dichloromethane, It mixed with the homogenizer and the W/O type emulsified matter was obtained. Next operation obtained the microcapsule like Example 1 except adding 0.5 g of D-mannitol to dispersion liquid. The content of the peptide A in 5 thru/or 60 mum, and a microcapsule of the particle size distribution of the microcapsule was 11.7% (w/w).

[0041]The microcapsule was obtained like Example 7 except the quantity of 1 ml and dichloromethane being the quantity of 1125 mg and distilled water 6.3 ml for the quantity of acetate of the example 8 peptide A. The content of the peptide A in 5 thru/or 60 mum, and a microcapsule of the particle size distribution of the microcapsule was 14.6% (w/w).

[0042]The microcapsule was obtained like Example 7 except the quantity of 1.2 ml and dichloromethane being the quantity of 1421 mg and distilled water 6.7 ml for the quantity of acetate of the example 9 peptide A. The content of the peptide A in 5 thru/or 60 mum, and a microcapsule of the particle size distribution of the microcapsule was 17.5% (w/w).

[0043]The microcapsule was obtained like Example 8 100.1% of the example except adding 50 g of D-mannitol into 1,000 ml of PVA solutions. The content of the peptide A in 5 thru/or 60 mum, and a microcapsule of the particle size distribution of the microcapsule was 14.7% (w/w).

[0044]The microcapsule was obtained like Example 9 110.1% of the example except adding 50 g of D-mannitol into 1,000 ml of PVA solutions. The content of the peptide A in 5 thru/or 60 mum, and a microcapsule of the particle size distribution of the microcapsule was 17.0% (w/w).

[0045]1125 mg of acetate of the reference example 1 peptide A, and PLGA (the Wako Pure Chem make.) lot.950526, lactic acid/glycolic acid (mole ratio): Number average molecular weight:3,800 4.5g by 74/26, GPC weight-average-molecular-weight:11,700, GPC number average molecular weight:5,200, and end group analysis was dissolved in 6.0 ml of dichloromethane. After cooling this solution at 16 **, it poured in into 1000 ml of 0.1% polyvinyl alcohol (EG-40, product made from Japanese synthetic chemistry) solution beforehand cooled at 16 **, and was considered as the O/W type emulsified matter by 7000 rpm using the turbine type homomixer (product made from the formation of a special opportunity). After agitating this O/W type emulsified matter at

the room temperature for 3 hours and vaporizing dichloromethane, it centrifuged by 2000 rpm using the centrifuge (05PR-22, Hitachi). Dispersion liquid were further centrifuged for the sediment obtained after re dispersion to distilled water, and washing removal of the releaser thing was carried out. The obtained microcapsule was added to a little distilled water, 0.5 g of D-mannitol was added to dispersion liquid after re dispersion, it freeze-dried and the microcapsule was obtained as powder. The content of the peptide A in 5 thru/or 60 mum, and a microcapsule of the particle size distribution of the microcapsule was 13.2% (w/w).

[0046]The microcapsule was obtained like the reference example 1 except the quantity of 1421 mg and dichloromethane being 6.2 ml the quantity of acetate of the reference example 2 peptide A. The content of the peptide A in 5 thru/or 60 mum, and a microcapsule of the particle size distribution of the microcapsule was 15.9% (w/w).

[0047]The microcapsule was obtained like the reference example 2 30.1% of the reference example except adding 50 g of D-mannitol into 1,000 ml of PVA solutions. The content of the peptide A in 5 thru/or 60 mum, and a microcapsule of the particle size distribution of the microcapsule was 15.5% (w/w).

[0048]microcapsule abbreviation 20 mg obtained in example of experiment 1 Example 4 -- a dispersing solvent (carboxymethyl cellulose of 2.5 mg.) 0.5 It distributed to distilled water 0.5 ml which dissolved mannitol of polysorbate 80 of mg, and 25 mg, and the regions-of-back hypodermic of the 10-week old male SD rat was medicated with 22G hypodermic needle. The microcapsule which slaughters a rat for every after-administration fixed time, and remains to an administration part is taken out, and, in the bottom, a result is shown for the peptide A in this taken-out microcapsule in Table 1 in fixed quantity.

[Table 1]

---------- time Peptide A survival rate (%)

---------- One day 96.41 weeks 84.82 weeks 59.23 week 38.84 week 24.6 ---------- As shown in the result of Table 1, in the microcapsule obtained by this invention manufacturing method, there is almost no initial burst and the peptide A is emitted regularly.

[0049]

[Effect of the Invention]According to the manufacturing method of this invention, it is peptide. [I]Or the sustained release drug containing the salt is easy, and is obtained with good yield. The sustained release drug obtained by this manufacturing method is peptide. [I] The steady discharge over a long period of time is shown, and an excessive amount of drug release immediately after administration can be controlled. In particular, it is peptide after sustained release drug administration. [I] The histamine isolation operation to depend is inhibited. To light, heat, humidity, coloring, etc., the sustained release drug obtained by the manufacturing method of this invention is stable, and excellent in preservation stability. In manufacture of the sustained release drug which has the same discharge pattern especially, In the W/O/W method of this invention, since a molecular weight can use higher biodegradation nature polymer of glass transition temperature more greatly as compared with the conventional O/W method, the sustained release drug superior to that of preservation stability can be manufactured.